IN THE CLAIMS:

A clean version of all amended claims is provided herewith in **Attachment D**. It will be noted that the claims have been amended relative to the previously provided version as shown by the marked up version thereof in **Attachment E** provided herewith.

REMARKS

Claims 1-7, 9, 10, 14-17 and 20-35 stand pending in the present application. By this amendment, Applicants have amended claims 1-7, 9, 10, 14-17, 20-22, 24-27, 28-35 and canceled claims 16 and 17. Applicants respectfully traverse the rejection to claims based on the discussion that follows.

The Examiner noted that the declaration was defective for failing to include the citizenship of every inventor. Applicants are preparing a Supplemental Declaration to be executed by inventor Quach which includes his citizenship. As soon as Applicant receives the executed supplemental declaration, Applicant will file the executed declaration with the U.S. Patent and Trademark Office.

The Examiner raised an objection to claims 30-32 stating that the specification as originally filed failed to provide support for "diagnostic substrate". Applicant respectfully submits that although the term is not expressly stated in the specification, the specification supports the expression "diagnostic substrate". Specifically, the specification from page 10, line 30 to page 12, line 3 describes that an ULIP polypeptide, optionally attached to a solid support, allows for the detection of PNS in cancers when combined with appropriate means of detection/visualization. Further, the specification refers to a "kit", on page 11, line 22. Therefore, one of ordinary skill in the

art would expect a kit, as described in the specification and in the context of the present disclosure, would include a set of reagents and visualization components. Therefore, the term "diagnostic substrate" is supported by the specification as filed.

Further, Applicants respectfully submit that the term "substrate" would be understood by one of ordinary skill in the art and consistent with the context of the present disclosure to mean "reagent".

Based on the foregoing discussions, Applicants respectfully request that the Examiner withdraw the objection to claims 30-32 as not being supported by the specification as filed.

The Examiner rejected claim 10 under 35 U.S.C. §101 for failing to set forth steps involved in the process. By this amendment, Applicants have amended claim 10 to obviate the rejection to claim 10 under 35 U.S.C. §101.

The Examiner rejected claims 1-7, 9, 10, 14-17 and 20-35 under 35 U.S.C. §112, first paragraph, stating that the claims are drawn to a polypeptide of SEQ ID No. 8 inconsistent with the polynucleotide sequence SEQ ID No. 7 which encodes SEQ ID No. 8. By this amendment, Applicants have submitted a substitute Sequence Listing which corrects inadvertent deficiencies present in SEQ ID No. 8 as filed.

Referring to the discrepancies between SEQ ID Nos. 7 and 8 in further detail, the Examiner accurately notes the discrepancy between SEQ ID No. 8 and Figure 12. Two inadvertent clerical errors have been made in the authoring of the present application with regard to ULIP-4 amino acid sequence of SEQ ID No. 8.

First, Figure 12 describes an ULIP-4 polypeptide containing 553 amino acids. One of these, in position 56, is marked with an asterisk. As discussed in the

specification at page 18, lines 23-30, the corresponding TAG codon is actually an error of the reverse transcriptase enzyme. By comparison with the rat and mouse ULIP-4 proteins, the inventors noticed that the residue in position 56 belongs to a conserved region of the ULIP-4 sequence and concluded that the asterisk should be replaced by a lysine (page 18, line 28).

Unfortunately, a clerical error occurred in the preparation of the sequence listing where the intended lysine 56 of SEQ ID No. 8 was inadvertently changed to histidine. Thus, enclosed herewith is a substitute sequence listing wherein amino acid 56 of SEQ ID No. 8 is now correctly identified as lysine.

Secondly, SEQ ID No. 8 is 572 amino acids long whereas Figure 12 contains only 553 amino acids. The carboxy end of human ULIP-4 protein was deduced from its rat and mouse counterparts, as disclosed at page 18, lines 31-35 at the present application. The second clerical error made is that SEQ ID No. 8 was completed with 19 amino acids (572-553), not 15 amino acids as is indicated in the specification.

Mouse ULIP-4 polypeptide sequence is actually depicted in Figure 11 and SEQ ID No. 6. Both sequences contain 572 amino acids. Since the Figure 12 sequence was completed according to mouse and rat ULIP-4 sequences, the complete human ULIP-4 protein should contain 572 amino acids, as it is accurately indicated in SEQ ID No. 8.

Therefore, based on the foregoing discussion and the disclosure in the specification with regard to SEQ ID Nos. 7 and 8, Applicants respectfully request the Examiner to withdraw the rejection to the claims under 35 U.S.C. §112, first paragraph.

The Examiner objected to the claims, indicating that the claims have to further be restricted to one of the sequences SEQ ID No. 2, 4, 6 or 8. By this amendment,

Applicants have amended the claims to be specifically directed to a purified ULIP polypeptide comprising an amino acid sequence listed from SEQ ID No. 2, 4, 6 and 8. Applicants respectfully submit that SEQ ID No. 2, 4, 6 and 8 all relate to a purified ULIP polypeptide family and therefore present unity of invention in accordance with 37 C.F.R. §1.499 and the unity of invention standard under 37 C.F.R. §1.475(b)(3). Therefore, Applicants respectfully request that the Examiner withdraw the further restriction of the claims to a single sequence, SEQ ID No. 2, 4, 6 or 8.

The Examiner rejected claim 10 under 35 U.S.C. §112, first paragraph, stating that the specification, while being enabling for a method for using the polypeptide of SEQ ID No. 8 or derivative thereof, to detect the presence of anti-CV2 antibodies in a biological sample wherein the sample is blood serum or cerebral spinal fluid (CSF), the specification does not reasonably provide enablement for a method for using any fragment of the polypeptide of SEQ ID No. 8 or a nucleic acid molecule comprising the polynucleotide sequence of SEQ ID No. 7 to detect the presence of anti-CV2 antibodies in any biological sample.

Applicants respectfully submit that claim 10 is properly supported in the specification to enable one of ordinary skill in the art to practice the invention as claimed. Although the Examiner states that the specification does not enable one skilled in the art to determine which fragments of the polypeptide SEQ ID No. 8 would allow for the detection of anti-CV2 antibodies, the Examiner does admit that the fragment, which can be used for detection, can also be determined empirically. Therefore, this implies that it is routine and does not require further discovery of invention or undue experimentation for one of ordinary skill in the art to determine an

appropriate fragment of the polypeptide SEQ ID No. 8. Thus, Applicants respectfully submit that the disclosure in the specification is sufficient to allow one of ordinary skill in the art to carry out and practice the invention commensurate in scope with the claims.

Furthermore, since at least one antigenic fragment of ULIP-4 is disclosed in the specification, see e.g. page 5, lines 26-28, any fragment containing this antigen could be suitable to carry out the claimed invention. Based on the foregoing, Applicants respectfully request that the Examiner withdraw the rejection to claim 10 under 35 U.S.C. §112, first paragraph.

The Examiner rejected claims 9, 13-17 and 33-35 under 35 U.S.C. §112, first paragraph. The Examiner acknowledges enablement for the detection of PNS and/or tumors involving expression of anti-CV2 antibodies. However, the Examiner's position is that the present invention does not enable for the detection of any tumor. Applicants respectfully disagree with the Examiner's position as the claimed diagnostic methods can allow for detection of any tumor provide anti-CV2 antibodies are expressed. Therefore, the scope of the claims are clearly limited by the recited condition, namely that the specific immunological complexes are "indicative of a paraneoplastic neurological syndrome and/or of a tumor".

With respect to the rejection of claims 16-17 under 35 U.S.C. §112, first paragraph, Applicants have canceled claims 16-17 without addressing the merits of the 35 U.S.C. §112, first paragraph rejection in order to expedite prosecution and move this application to allowance.

Regarding claims 30-32, these claims are directed to a diagnostic substrate (i.e., a reagent) for *ex vivo* diagnosis and not a method of diagnosis as thought by the

Examiner. For example, in claim 31, the support, comprising animal brain, includes fixed brain sections. Applicants have amended claims 30-32 to more specifically and succinctly claim Applicants invention which is drawn to a reagent for *ex vivo* diagnosis and to a method of diagnosis as was originally believed by the Examiner.

In view of the foregoing, Applicants respectfully submit that the amendment to the claims and the foregoing discussion obviate the rejection to claims 9, 13-15 and 33-35.

Claims 1-7, 9, 10, 14-17 and 20-30 were rejected under 35 U.S.C. §112, first paragraph on the grounds that the specification does not reasonably convey to one skilled in the relevant art that the Applicants, at the time of the application was filed, possessed the claimed invention. Further, the Examiner indicates that the written description includes more than one disparate disclosure and that the claims are drawn to a genus and no species is adequately described. In addition, the Examiner indicates that the specification fails to describe the physical features of a sufficient number of species to reasonably convey to one skilled in the art that the Applicants had possession of the invention at the time the application was filed.

Contrary to the Examiner's assertion, Applicants respectfully submit that the specification, as filed, does provide sufficient description to convey to one of ordinary skill in the art that the Applicants had possession of the claimed invention at the time the application was filed. Moreover, Applicants respectfully submit that the amendment to the claims more clearly and succinctly claim what Applicants believe to be the invention which, based on the foregoing discussion, is fully supported in the specification as filed. Therefore, Applicants submit that the specification, as filed, conveys to one of ordinary

skill in the art that the Applicants possessed the present invention as now claimed. Thus, Applicants respectfully request that the Examiner withdraw the rejection to claims 1-7, 9, 10, 14-17 and 20-35 under 35 U.S.C. §112, first paragraph.

The Examiner rejected claims 1-7, 9, 10, 14-17 and 20-35 under 35 U.S.C. §112, second paragraph. By this amendment, Applicants have amended the claims to obviate the rejection under 35 U.S.C. §112, second paragraph.

Claims 1-5 were rejected under 35 U.S.C. §102(b) as being anticipated by Hamajima et al. (gene 180) 157-163, 1996. Contrary to the Examiner's assertion, claims 1-5 are not anticipated by Hamajima. Hamajima et al. discloses the sequence of three proteins, human DRP1, 2 and 3, that actually correspond to human ULIP-3, 2 and 1, respectively as indicated in Table I of the present specification (see page 27). SEQ ID No. 7 and 8 are the nucleic acid and amino acid sequences of human ULIP-4 respectively and therefore novel over and not anticipated by Hamajima.

To further support this assertion, enclosed herewith is a sequence alignment of human ULIP-1, 2, 3 and 4 cDNA sequences that illustrates that ULIP-4 differs from the three previously identified ULIP disclosed in Hamajima et al.

In view of the foregoing, Applicants respectfully request that the Examiner withdraw the 35 U.S.C. §102(a) rejection of claims 1-5 by Hamajima.

Claims 1-7, 9, 10, 14, 15, 20-24 and 33-35 were rejected under 35 U.S.C. §103(a) as being unpatentable over Hamajima individually or in combination with Honnorat et al. and Antoine et al., U.S. Patent Nos. 5,770,381 and 6,066,475.

Applicants respectfully submit that the present claims are not anticipated by the aforementioned references. Claims 1-5 recite further novel elements not disclosed nor

suggested by Hamajima et al. In fact, from Hamajima, it is not possible to deduce that a fourth member of the ULIP family might exist. Therefore, there would not have been any incentive for a person skilled in the art to try to identify another ULIP protein.

Regarding the *prima facie* obviousness rejection over Honnorat et al. and Antoine et al., Applicants respectfully submit that such a conclusion of obviousness could only be reached from an unacceptable hindsight analysis. As is described in the present specification and discussed below, it was only after a succession of observations that the inventors were able to clone ULIP-4.

Briefly explaining the experimental procedures which lead to discovery and cloning of the ULIP-4 gene, proteins from rat brain extracts, separated by isofocalization, were blotted on a membrane. Incubation of the membrane with anti-CV2 antibodies indicated that several bands were recognized by the antibodies. An additional electrophoresis allowed isolation of a protein having a molecular weight of 66 kDa. Trypsin digestion of the isolated protein generated seven peptide sequences that surprisingly showed homology with ULIP-1 and ULIP-2, as was evidenced by sequence alignment with protein databases.

The inventors then expressed recombinant ULIP-1, ULIP-2 and ULIP-3 in *E. coli*. A Western Blot analysis with anti-CV2 antibodies which revealed that none of the three known ULIP proteins could be recognized in the experiment conditions.

A search in databases lead to the identification of a partial human clone ATCC No. 426430, showing some homology with the cDNA sequences of ULIP-1, 2 and 3, but still different from these sequences. This partial clone, as well as ULIP-2 and ULIP-3, were further used for the screening of a λ Zap II cDNA bank of new-born mice brain.

This screening generated several complete sequences, one of which corresponded to an unknown fourth member of the ULIP protein family: ULIP-4.

Afterwards, HeLa cells transfected with ULIP-4 cDNA were demonstrated to be specifically recognized by anti-CV2 antibodies whereas ULIP-1-3 were not. However, *E. coli* expressed ULIP-4 did not react with anti-CV2 antibodies, which indicated that ULIP-4 epitope bears a post-translational modification.

In light of the above explanation regarding the experimental procedure followed by the inventors to clone ULIP-4 cDNA, the present invention is non-obvious over Honnorat et al. and Antoine et al. for the following reasons.

Honnorat et al. teaches that antibodies called "anti-CV2 antibodies" from patients with paraneoplastic neurological syndromes, react with a 66 kDa band of a *post-mortem* protein extract from rat and human brain.

This 66 kDa band is not purified and therefore, according to our above indications, comprises at least a mix of ULIP-1, 2, 3 and 4, all ULIPs having the same molecular weight.

It was therefore impossible to deduce the nature of the antigen recognized by the anti-CV2 antibodies from the teaching of Honnorat et al.

The presence of a post-translational modification within the ULIP-4 epitope made it difficult to achieve antigen identification since it was conditioned by the system chosen for the recombinant protein expression.

Moreover, it is respectfully noted that bacterial expression systems, such as *E. coli*, do not allow for post-translational modifications of recombinant proteins herein expressed. Therefore, ULIP-4 epitope could only have been detected using the

mammalian transfection HeLa cells. Since ULIP-1, 2, 3 expressed in *E. coli* recognize anti-CV2 antibodies, there was no teaching or indication that an additional member of the ULIP family, if it even exists, would bear a post-translational modification in the epitopic sequence, reacting with anti-CV2 antibodies.

As a consequence, nothing in the prior art would have provided motivation for one skilled in the art to choose HeLa cells to try to express the new protein reacting with anti-CV2 antibodies.

In conclusion, the claims are not anticipated by nor made obvious from Hamajima et al. Moreover, nothing in Honnorat et al. or Antoine et al. would have further assisted one skilled in the art to achieve ULIP-4 cloning. Accordingly, the subject-matter of the pending claims are novel and not obvious over the prior art. Therefore, based on the foregoing discussion, Applicants respectfully submit that the claims are not anticipated by the aforementioned references and therefore the 35 U.S.C. §103(a) rejection to the claims should be withdrawn.

In view of the foregoing discussion, Applicants respectfully submit that the present application is now in condition for immediate allowance.

Respectfully submitted,

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